# *ABC of heart failure*
# Pathophysiology

G Jackson, C R Gibbs, M K Davies, G Y H Lip

Heart failure is a multisystem disorder which is characterised by abnormalities of cardiac, skeletal muscle, and renal function; stimulation of the sympathetic nervous system; and a complex pattern of neurohormonal changes.

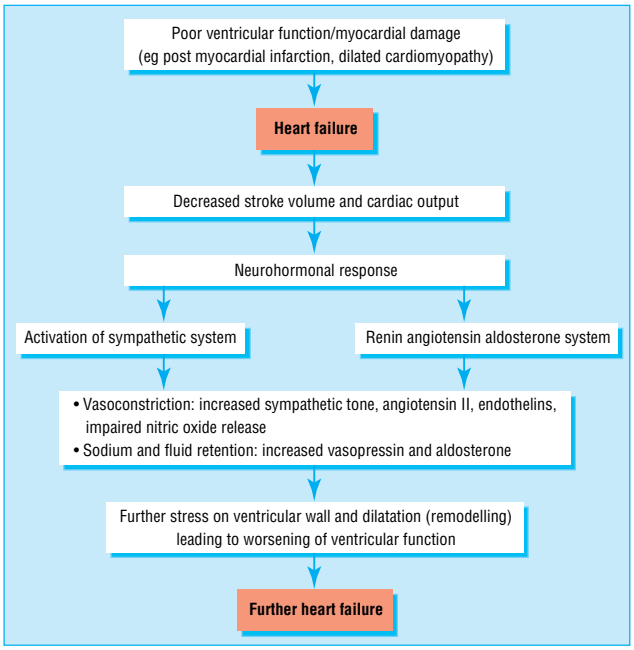
**Developments in our understanding of the pathophysiology of heart failure have been essential for recent therapeutic advances in this area**

## Myocardial systolic dysfunction

The primary abnormality in non-valvar heart failure is an impairment in left ventricular function, leading to a fall in cardiac output. The fall in cardiac output leads to activation of several neurohormonal compensatory mechanisms aimed at improving the mechanical environment of the heart. Activation of the sympathetic system, for example, tries to maintain cardiac output with an increase in heart rate, increased myocardial contractility, and peripheral vasoconstriction (increased catecholamines). Activation of the renin-angiotensin-aldosterone system (RAAS) also results in vasoconstriction (angiotensin) and an increase in blood volume, with retention of salt and water (aldosterone). Concentrations of vasopressin and natriuretic peptides increase. Furthermore, there may be progressive cardiac dilatation or alterations in cardiac structure (remodelling), or both.

## Neurohormonal activation

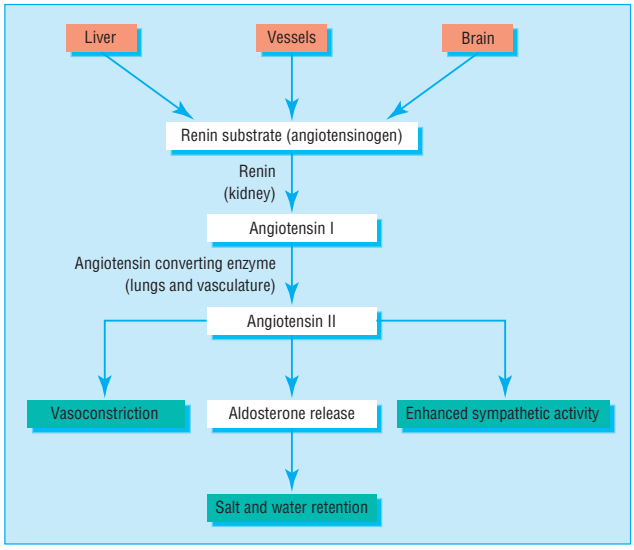
Chronic heart failure is associated with neurohormonal activation and alterations in autonomic control. Although these compensatory neurohormonal mechanisms provide valuable support for the heart in normal physiological circumstances, they also have a fundamental role in the development and subsequent progression of chronic heart failure.




Neurohormonal mechanisms and compensatory mechanisms in heart failure

### Renin-angiotensin-aldosterone system

Stimulation of the renin-angiotensin-aldosterone system leads to increased concentrations of renin, plasma angiotensin II, and aldosterone. Angiotensin II is a potent vasoconstrictor of the renal (efferent arterioles) and systemic circulation, where it stimulates release of noradrenaline from sympathetic nerve terminals, inhibits vagal tone, and promotes the release of aldosterone. This leads to the retention of sodium and water and the increased excretion of potassium. In addition, angiotensin II has important effects on cardiac myocytes and may contribute to the endothelial dysfunction that is observed in chronic heart failure.




Renin-angiotensin-aldosterone axis in heart failure

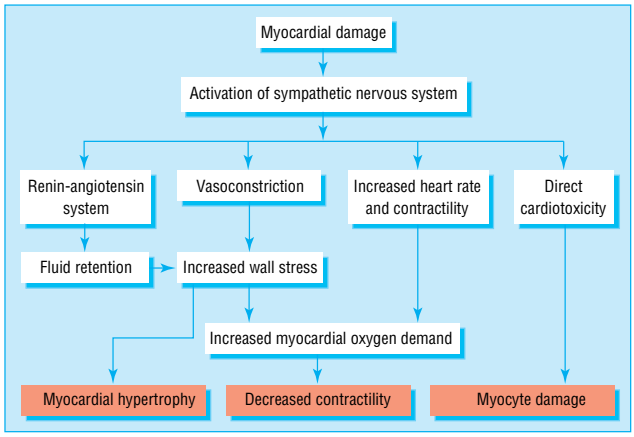
### Sympathetic nervous system

The sympathetic nervous system is activated in heart failure, via low and high pressure baroreceptors, as an early compensatory mechanism which provides inotropic support and maintains cardiac output. Chronic sympathetic activation, however, has deleterious effects, causing a further deterioration in cardiac function.

The earliest increase in sympathetic activity is detected in the heart, and this seems to precede the increase in sympathetic outflow to skeletal muscle and the kidneys that is present in advanced heart failure. Sustained sympathetic stimulation activates the renin-angiotensin-aldosterone system and other neurohormones, leading to increased venous and arterial tone

(and greater preload and afterload respectively), increased plasma noradrenaline concentrations, progressive retention of salt and water, and oedema. Excessive sympathetic activity is also associated with cardiac myocyte apoptosis, hypertrophy, and focal myocardial necrosis.

In the long term, the ability of the myocardium to respond to chronic high concentrations of catecholamines is attenuated by a down regulation in β receptors, although this may be associated with baroreceptor dysfunction and a further increase in sympathetic activity. Indeed, abnormalities of baroreceptor function are well documented in chronic heart failure, along with reduced parasympathetic tone, leading to abnormal autonomic modulation of the sinus node. Moreover, a reduction in heart rate variability has consistently been observed in chronic heart failure, as a result of predominantly sympathetic and reduced vagal modulation of the sinus node, which may be a prognostic marker in patients with chronic heart failure.



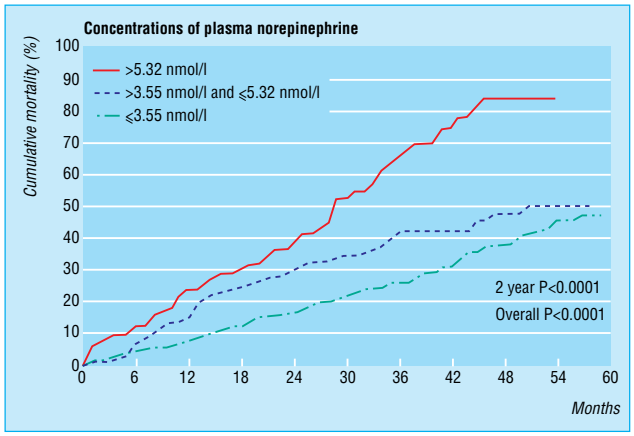

Sympathetic activation in chronic heart failure

### Natriuretic peptides

There are three natriuretic peptides, of similar structure, and these exert a wide range of effects on the heart, kidneys, and central nervous system.

Atrial natriuretic peptide (ANP) is released from the atria in response to stretch, leading to natriuresis and vasodilatation. In humans, brain natriuretic peptide (BNP) is also released from the heart, predominantly from the ventricles, and its actions are similar to those of atrial natriuretic peptide. C-type natriuretic peptide is limited to the vascular endothelium and central nervous system and has only limited effects on natriuresis and vasodilatation.

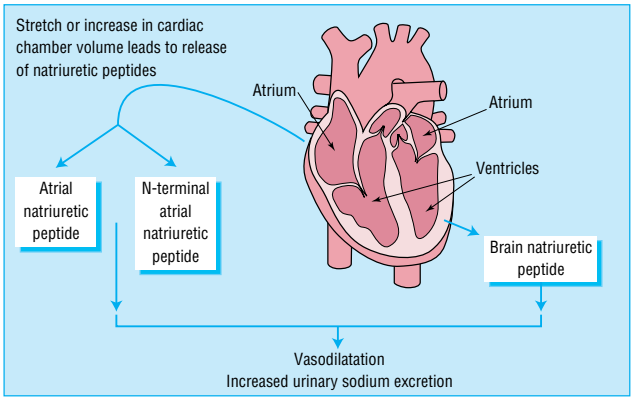
The atrial and brain natriuretic peptides increase in response to volume expansion and pressure overload of the heart and act as physiological antagonists to the effects of angiotensin II on vascular tone, aldosterone secretion, and renal-tubule sodium reabsorption. As the natriuretic peptides are important mediators, with increased circulating concentrations in patients with heart failure, interest has developed in both the diagnostic and prognostic potential of these peptides. Substantial interest has been expressed about the therapeutic potential of natriuretic peptides, particularly with the development of agents that inhibit the enzyme that metabolises atrial natriuretic peptide (neutral endopeptidase), and non-peptide agonists for the A and B receptors.




Norepinephrine concentrations and prognosis in chronic heart failure

### Antidiuretic hormone (vasopressin)

Antidiuretic hormone concentrations are also increased in severe chronic heart failure. High concentrations of the hormone are particularly common in patients receiving diuretic treatment, and this may contribute to the development of hyponatraemia.




Effects of natriuretic peptides

### Endothelins

Endothelin is secreted by vascular endothelial cells and is a potent vasoconstrictor peptide that has pronounced vasoconstrictor effects on the renal vasculature, promoting the retention of sodium. Importantly, the plasma concentration of endothelin-1 is of prognostic significance and is increased in proportion to the symptomatic and haemodynamic severity of heart failure. Endothelin concentration is also correlated with indices of severity such as the pulmonary artery capillary wedge pressure, need for admission to hospital, and death.

In view of the vasoconstrictor properties of endothelin, interest has developed in endothelin receptor antagonists as cardioprotective agents which inhibit endothelin mediated vascular and myocardial remodelling.

### Other hormonal mechanisms in chronic heart failure

- The arachidonic acid cascade leads to increased concentrations of prostaglandins (prostaglandin $E_2$ and prostaglandin $I_2$), which protect the glomerular microcirculation during renal vasoconstriction and maintain glomerular filtration by dilating afferent glomerular arterioles
- The kallikrein kinin system forms bradykinin, resulting in both natriuresis and vasodilatation, and stimulates the production of prostaglandins
- Circulating concentrations of the cytokine tumour necrosis factor (αTNF) are increased in cachectic patients with chronic heart failure. αTNF has also been implicated in the development of endothelial abnormalities in patients with chronic heart failure

## Patterns of neurohormonal activation and prognosis

**Asymptomatic left ventricular dysfunction**

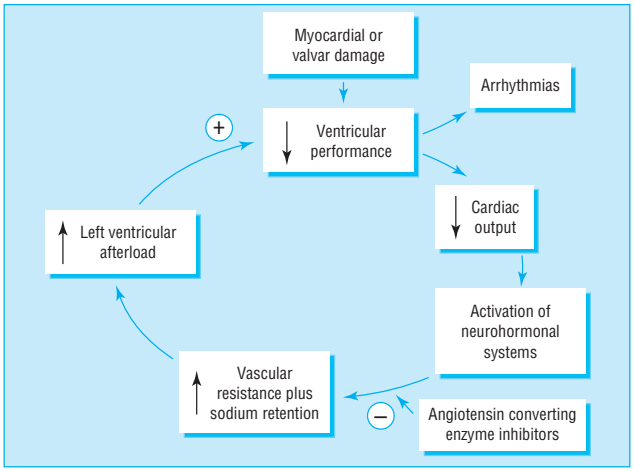
Plasma norepinephrine concentrations increase early in the development of left ventricular dysfunction, and plasma renin activity usually increases in patients receiving diuretic treatment. Norepinephrine concentration in asymptomatic left ventricular dysfunction is a strong and independent predictor of the development of symptomatic chronic heart failure and long term mortality. Plasma concentrations of N-terminal proatrial natriuretic peptide and brain natriuretic peptide also seem to be good indicators of asymptomatic left ventricular dysfunction and may be useful in the future as an objective blood test in these patients.

**Congestive heart failure**

In severe untreated chronic heart failure, concentrations of renin, angiotensin II, aldosterone, noradrenaline, and atrial natriuretic peptide are all increased. Plasma concentrations of various neuroendocrine markers correlate with both the severity of heart failure and the long term prognosis. For example, raised plasma concentrations of N-terminal and C-terminal atrial natriuretic peptide and of brain natriuretic peptide are independent predictors of mortality in patients with chronic heart failure. Patients with congestive heart failure and raised plasma noradrenaline concentrations also have a worse prognosis.

**After myocardial infarction**

- Plasma noradrenaline is of prognostic value in patients early after myocardial infarction, predicting subsequent changes in left ventricular volume
- Natriuretic peptides have also been shown to predict outcome after myocardial infarction, although it is not clear whether the predictive value is additive to measurements of ventricular function

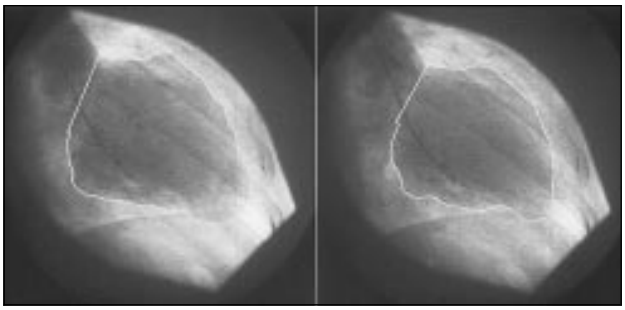



Effect of angiotensin converting enzyme inhibitors in heart failure

## Other non-cardiac abnormalities in chronic heart failure

**Vasculature**

The vascular endothelium has an important role in the regulation of vascular tone, releasing relaxing and contracting factors under basal conditions or during exercise. The increased peripheral resistance in patients with chronic heart failure is related to the alterations in autonomic control, including heightened sympathetic tone, activation of the renin-angiotensin-aldosterone system, increased endothelin concentrations, and impaired release of endothelium derived relaxing factor (or nitric oxide). There is emerging evidence that impaired endothelial function in chronic heart failure may be improved with exercise training and drug treatment, such as angiotensin converting enzyme inhibitors.



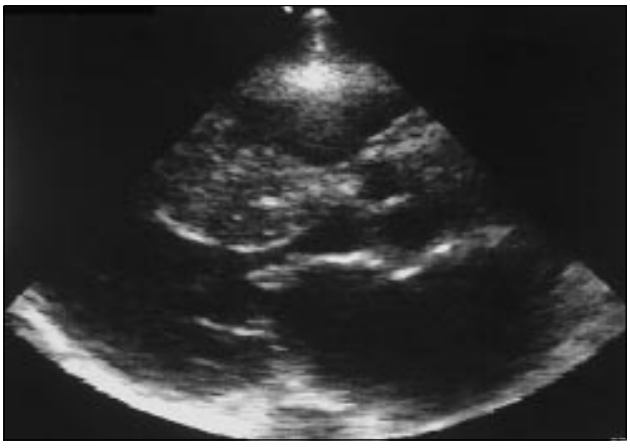
Contrast left ventriculogram in patient with poor systolic function (diastolic (left) and systolic (right) views)

**Skeletal muscle changes**

Considerable peripheral changes occur in the skeletal muscle of patients with chronic heart failure. These include a reduction in muscle mass and abnormalities in muscle structure, metabolism, and function. There is also reduced blood flow to active skeletal muscle, which is related to vasoconstriction and the loss in muscle mass. All these abnormalities in skeletal muscles, including respiratory muscles, contribute to the symptoms of fatigue, lethargy, and exercise intolerance that occur in chronic heart failure.

## Diastolic dysfunction

Diastolic dysfunction results from impaired myocardial relaxation, with increased stiffness in the ventricular wall and reduced left ventricular compliance, leading to impairment of diastolic ventricular filling. Infiltrations, such as amyloid heart disease, are the best examples, although coronary artery



Two dimensional echocardiogram in patient with hypertrophic cardiomyopathy showing asymmetrical septal hypertrophy

disease, hypertension (with left ventricular hypertrophy), and hypertrophic cardiomyopathy are more common causes.

The incidence and contribution of diastolic dysfunction remains controversial, although it has been estimated that 30-40% of patients with heart failure have normal ventricular systolic contraction. Indices of diastolic dysfunction can be obtained non-invasively with Doppler echocardiography or invasively with cardiac catheterisation and measurement of left ventricular pressure changes. There is no agreement as to the most accurate index of left ventricular diastolic dysfunction, but the Doppler mitral inflow velocity profile is probably the most widely used.

Although pure forms exist, in most patients with heart failure both systolic and diastolic dysfunction can be present. Knowing about diastolic dysfunction, however, has little effect on management of most patients with chronic heart failure, as there are still many uncertainties over its measurement and optimal management strategies.

## Myocardial remodelling, hibernation, and stunning

After extensive myocardial infarction, cardiac contractility is frequently impaired and neurohormonal activation leads to regional eccentric and concentric hypertrophy of the non-infarcted segment, with expansion (regional thinning and dilatation) of the infarct zone. This is known as remodelling. Particular risk factors for this development of progressive ventricular dilatation after a myocardial infarction include a large infarct, anterior infarctions, occlusion (or non-reperfusion) of the artery related to the infarct, and hypertension.

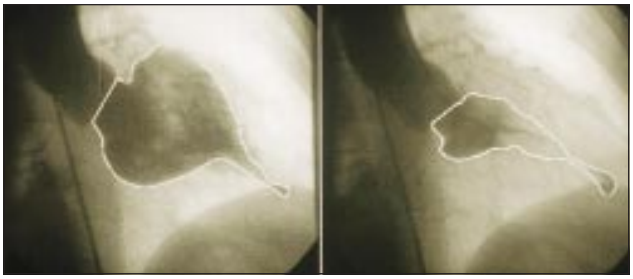
Myocardial dysfunction may also occur in response to "stunning" (postischaemic dysfunction), which describes delayed recovery of myocardial function despite restoration of coronary blood flow, in the absence of irreversible damage. This is in contrast to "hibernating" myocardium, which describes persistent myocardial dysfunction at rest, secondary to reduced myocardial perfusion, although cardiac myocytes remain viable and myocardial contraction may improve with revascularisation.

When stunning or hibernation occurs, viable myocardium retains responsiveness to inotropic stimulation, which can then be identified by resting and stress echocardiography, thallium scintigraphy and positron emission tomography. Revascularisation may improve the overall left ventricular function with potential beneficial effects on symptoms and prognosis.

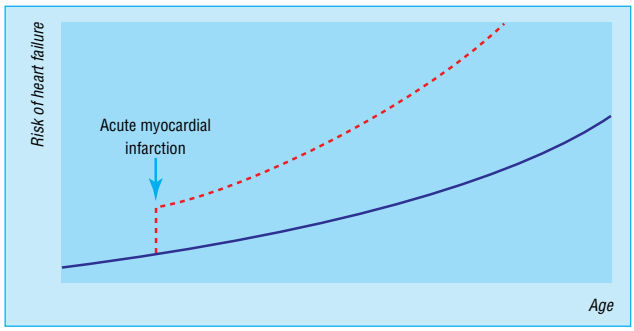

**Key references**

- Grossman W. Diastolic dysfunction in congestive heart failure. *N Engl J Med* 1991;325:1557-64.
- Love MP, McMurray JJV. Endothelin in heart failure: a promising therapeutic target. *Heart* 1997;77:93-4.
- McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, et al. Biochemical detection of left ventricular systolic dysfunction. *Lancet* 1998;351:9-13.
- Rahimtoola SH. The hibernating myocardium. *Am Heart J* 1989;117:211-21.
- Wilkins MR, Redondo J, Brown LA. The natriuretic-peptide family. *Lancet* 1997;349:1307-10.
- Packer M. The neurohormonal hypothesis: a theory to explain the mechanisms of disease progression in heart failure. *J Am Coll Cardiol* 1992;20:248-54.

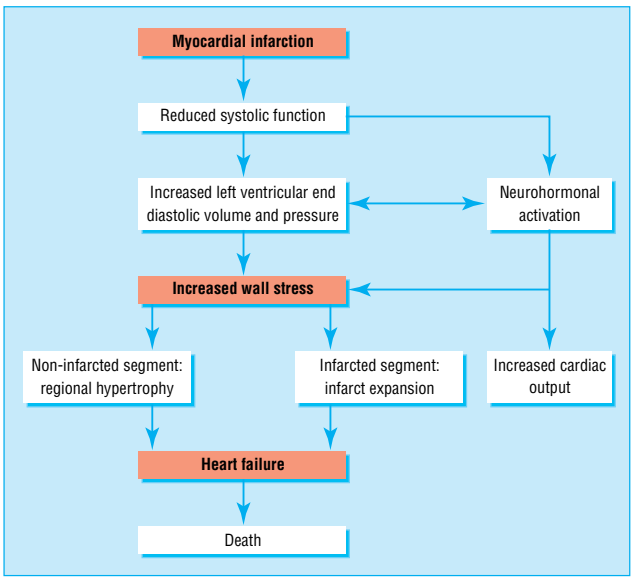

The graph showing mortality curves is adapted from Cohn et al (*N Engl J Med* 1984;311:819-23); the diagram of the process of ventricular remodelling is adapted from McKay et al (*Circulation* 1986;74:693-702).



Contrast left ventriculogram in patient with hypertrophic cardiomyopathy (diastolic (left) and systolic (right) views)




Risk of heart failure and relation with age and history of myocardial infarction




Process of ventricular remodelling


G Jackson is consultant cardiologist in the department of cardiology, Guy's and St Thomas's Hospital, London.


The ABC of heart failure is edited by C R Gibbs, M K Davies, and G Y H Lip. CRG is research fellow and GYHL is consultant cardiologist and reader in medicine in the university department of medicine and the department of cardiology, City Hospital, Birmingham; MKD is consultant cardiologist in the department of cardiology, Selly Oak Hospital, Birmingham. The series will be published as a book in the spring.

*BMJ* 2000;320:167-70